## REMARKS

Amendments to the Specification

Applicants have amended the paragraph at page 13, lines 13-24, of the specification to provide the complete serial number of the referenced, commonly owned, and co-filed, international application, i.e., PCT/US2004/008120 (Atty. Docket No.: NEU-101.1 PCT).

Amendments to the Claims

Applicants have amended Claim 1 to incorporate the limitations of original Claim 2, which is now canceled, to direct coverage in this application to a method of treating an impaired neurological function in an individual who has sustained a brain injury comprising administering to said individual an effective amount of modafinil (benzhydrylsulfinylacetamide) in conjunction with a neurorehabilitation program comprising one or more neurostimuli designed to enhance or restore said impaired neurological function. Applicants have also amended Claims 3, 4, 9, and 11 to adjust the dependency from original Claim 2 to Claim 1, as amended herein. Accordingly, the amendments add no new matter.

Applicants have canceled dependent Claims 17, 18, and 19 to eliminate redundancy with dependent Claims 14, 15, and 16, respectively. To conform the claims to U.S. practice, Applicants have also canceled Claims 26, 27, 28, and 29, which were written in a Swiss-style "use" format, which is not permissible under U.S. practice. Cancellation of any claim should not be interpreted as abandonment by Applicants of the subject matter recited in the canceled claim or in the specification. Applicants reserve the right to pursue patent coverage for any subject matter recited in any canceled claim or the specification in one or more continuation or divisional applications.

Applicants have also amended Claim 3 to clearly recite the embodiment of Claim 1 wherein the neurorehabilition program "is selected from the group consisting of physical therapy, occupational therapy, speech therapy, and combinations thereof". Support for the amendment is found in the specification. See, e.g., in the specification, page 6, lines 30-32. Accordingly, the amendment adds no new matter.

None of the amendments adds new matter, and entry of the amendments is respectfully requested.

Objection to the Specification

In the Office Action, dated September 6, 2007, the Examiner objected to the specification because the complete serial number of a commonly owned, co-filed, international application was not recited at page 13, line 23, of the specification. As indicated above and as instructed by the Examiner, Applicants have amended the specification by replacing the paragraph at page 13, lines 13-24 with one that recites the complete serial number of the referenced application, i.e., international application No. PCT/US2004/008120 (Atty. Docket No. NEU-101.1 PCT). Entry of the amendment is respectfully requested.

As the amendment to the specification renders the objection moot, Applicants respectfully request that the Examiner reconsider and withdraw the objection.

Rejection Under 37 C.F.R. § 112, second paragraph

In the Office Action, the Examiner objected to Claim 3 as vague and unclear for recitation of the phrase "combinations thereof". As noted above, Applicants have amended Claim 3 to cover those embodiments of the method of Claim 1 (as amended herein) wherein the neurorehabilitation program "is selected from the group consisting of" physical therapy, occupational therapy, speech therapy, and combinations thereof. Applicants respectfully submit that the amendment places Claim 3 in proper form under U.S. practice for reciting alternative embodiments and thereby renders the objection moot. Accordingly, reconsideration and withdrawal of the objection are respectfully requested.

Art-Based Rejections of the Claims

The Examiner rejected the claims as anticipated under 37 C.F.R. § 102 or as obvious under 37 C.F.R. § 103. Before addressing each of these rejections, Applicants provide the following overview of the claimed invention.

The Claimed Invention

As indicated above, Applicants have amended the claims to direct coverage in this application to a method of treating an impaired neurological function in an individual who has sustained a brain injury comprising administering to such an individual an effective amount of modafinil (benzhydrylsulfinylacetamide) in conjunction with a neurorehabilitation program that comprises one or more neurostimuli designed to enhance or restore one or more impaired neurological functions. Such a combination to treat brain-injured patients has not been previously taught or suggested in the art.

Previous attempts to improve the effectiveness of neurorehabilitation programs for treating an impaired neurological function in brain-injured patients have focused on the effects of known, traditional psychostimulants (neurostimulants, stimulants), such as amphetamines and methylphenidate (see, e.g., review by Whyte et al., *J. Head Trauma Rehabil., 17(4)*: 284-299 (2002)) or levodopa (L-dopa) (see, e.g., Scheidtmann et al., *Lancet, 358*: 787-790 (2001)). Modafinil is neither pharmacologically or chemically equivalent to these traditional stimulants or levodopa.

Traditional stimulants include such well known compounds as caffeine, D-amphetamine, and methylphenidate (active ingredient in Ritalin®). These compounds affect the sympathetic nervous and/or the CNS primarily by increasing norepinephrine and dopamine levels in the brain by reuptake inhibition (see, e.g., in the specification, page 8, lines 10-19; Lyons et al., *Aviat. Space Environ. Med., 62(5)*: 432-435 (1991) (abstract)). Well known effects of traditional stimulants include increased heart rate, increased respiration rate, increased blood pressure, and decreased appetite. Whyte (2002) mentions that traditional stimulants were commonly used in rehabilitation of individuals with traumatic brain injury,

despite a "dearth of well-controlled studies of their effects" (see, Whyte (2002), Background) and therefore conducted a search of the literature for controlled studies that might provide reliable and unbiased data in support of using traditional stimulants with neurorehabilitation. Whyte (2002) concludes that more randomized, placebo-controlled studies are needed to answer questions of efficacy of traditional psychostimulants to treat patients of traumatic brain injury (see, e.g., Whyte (2002), page 297). In fact, Treig et al. (*Clin. Rehabil., 17*: 590-599 (2003)), which was published after Applicants' priority date, addressed the various unreliable and contradictory reports of the use of traditional stimulants to treat brain-injured (stroke) patients by conducting a randomized placebo-controlled study of the effect of the paradigm stimulant D-amphetamine in conjunction with physiotherapy. Treig (2003) concluded that the stimulant provides no benefit when added to physiotherapy.

Levodopa increases the level of dopamine in the brain. The untoward side effects of chronic levodopa administration are known in the art from many years of treating Parkinson's Disease patients and include, but are not limited to, the classic, debilitating, levodopa-induced abnormal involuntary movement ("AIM", dyskinesis); nausea/vomiting; tremors; sialorrhea (drooling); headaches; dizziness; hallucinations; numbness; insomnia; and fatigue. Such side effects, and especially the levodopa-induced dyskinesis, eventually prevent further use of levodopa therapy (see, e.g., Column 1, lines 33-44, of Rise, cited in the Office Action). In fact, treatment of early stage Parkinson's Disease patients with levodopa is preferably postponed to avoid onset of levodopa-induced dyskinesis and other side effects that eventually foreclose further levodopa administration. See, e.g., Thanvi et al., *Postgrad. Med. J., 83(980)*: 384-388 (2007) (abstract); Müller et al., *Expert Opin. Pharmacother., 7(13)*: 1715-1730 (2006) (abstract)).

Scheidtmann (2001) states that a single dose of levodopa (L-dopa) administered to stroke patients in conjunction with an extensive physiotherapy regimen produced a greater improvement in motor function than in patients that received placebo and physiotherapy. The study in Scheidtmann (2001) looked for persistence of improved motor function for three weeks after providing the levodopa + physiotherapy combination. However, the aforementioned side effects of levodopa limit the application of this therapy. In particular, a therapy to treat an impaired neurological function in brain-injured patients is often repeated to restore or maintain the level of restored function. In fact, brain-injured patients may be treated with a neurorehabilitation programs for months or years to restore or maintain restoration of an impaired neurological function (see, e.g., Khan et al., *MJA, 178*: 290-295 (2003)). Following patients for only three weeks post treatment as in Scheidtmann (2001) may not be a sufficiently useful time period to assess any sustainable benefit. Moreover, repeated or continuous (chronic) administration of levodopa will inevitably induce the characteristic side effects in patients that eventually outweigh and foreclose further applications of the levodopa therapy. Scheidtmann (2001) does not address how the levodopa-based therapy might be maintained as the characteristic untoward side effects of continued levodopa

administration emerge in patients. However, it is notable that Scheidtmann (2001) teaches use of only a single dose of levodopa in combination with physiotherapy and then only as an "add-on" to other treatments (see, "Interpretation", page 787, Scheidtmann (2001)). In contrast, since repeated or long term administration of modafinil in humans is not linked to the development of debilitating levodopa-type side effects (see, e.g., Lyons et al., *Aviat. Space Environ. Med., 62(5)*: 432-435 (1991) (abstract); Hirshkowtiz et al., *CNS Drugs, 21*: 407-416 (2007) (abstract)), Applicants' claimed method may be used repetitively and/or chronically to treat brain-injured patients. This is a much needed improvement in methods of neurorehabilitative therapy.

Modafinil is not structurally, pharmacologically, or physiologically equivalent to either traditional neurostimulants or the compound levodopa (see, e.g., Wong et al., *J. Clin. Pharmacol., 39*: 30-40 (1999), especially paragraph bridging pages 30 and 31; Physician's Desk Reference, 58th edition, "PROVIGIL®", at pages 1160-1163 (Thompson PDR, Montvale, New Jersey, 2004); Physician's Desk Reference, 61st edition, "PARCOPA®", at pages 3097-3099 (Thompson PDR, Montvale, New Jersey, 2007)). Applicants have discovered that modafinil in conjunction with a neurorehabilitation program that is a more effective treatment instead of the failed prior art methods that employed a traditional stimulant in combination with a neurorehabilitation program (Whyte (2002); Treig (2003)). Applicants' claimed method of treatment is also safer and more useful with respect to long term and repetitive administrations than levodopa-based therapies, which place patients at risk of developing debilitating side effects, such as levodopa-induced AIM (dyskinesis).

Rejections Under 37 C.F.R. § 102

The Examiner rejected Claims 1, 2, 4, 7, 8, 14-23, and 25 under 37 C.F.R. § 102 as anticipated by U.S. Patent No. 6,492,396 ("Bacon"). In particular, the Examiner stated:

> "Regarding **claims 1, 2, 4, 7-8, 20-23, and 25**, Bacon teaches the treatment of multiple sclerosis, Parkinson's disease, and Alzheimer's disease as well as stroke using an effective amount of [modafinil] in combination with various agents including apomorphine and amphetamine (e.g., Col. 1, line 30-Col. 2, line 30; Col. 4, lines 30-40). . .
>
> "Regarding **claims 14-19**, Bacon additionally teaches the administration of a [modafinil] analog in preferred daily doses including 50, 100, and 200 mg/day. These doses fall within the range of 50 to 600 mg/day, and include a daily dose of 200 mg/day." (Office Action, page 3; bold in original)

Applicants respectfully traverse the rejections for the reasons explained below.

For anticipation under 35 U.S.C. § 102 by a printed publication, that publication must teach each and every element or aspect of the claimed invention. As explained in MPEP § 2131:

**"TO ANTICIPATE A CLAIM, THE REFERENCE MUST TEACH EVERY ELEMENT OF THE CLAIM**

> " 'A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference.' *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). 'The identical invention must be shown in as complete detail as is contained in the . . . claim.' *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." (emphasis in original).

Applicants' claimed invention provides a method of treating an impaired neurological function in an individual who has sustained a brain injury comprising administering to the individual an effective amount of modafinil in conjunction with a neurorehabilitation program.

Bacon states there is a need for novel classes of compounds that possess beneficial properties (Column 3, lines 9-24, of Bacon). Bacon's solution to this problem is to provide a new class of substituted thioacetamides to treat various diseases (Column 3, lines 31-34, of Bacon). The structural formulas of all of the substituted thioacetamides (formulas I and II) are clearly different from the structure of modafinil. A portion of the Background of the Invention of Bacon includes a review of modafinil (see, within Column 1, line 30-Column 2, line 12, of Bacon). However, Column 2, lines 13-30 and Column 4, lines 30-40 of Bacon, as cited by the Examiner, do not describe uses of modafinil but rather uses of derivatives and analogs of modafinil or the new substituted thioacetamide compounds of Bacon. Moreover, nowhere does Bacon provide any teaching of Applicants' claimed combination therapy, i.e., of treating an impaired neurological function in a brain-injured individual by administering to the individual an effective amount of modafinil in conjunction with a neurorehabilitation program. Since Bacon does not teach each and every element of amended Claim 1, or claims depending therefrom, Bacon does not qualify as a reference under 37 C.F.R. § 102. Accordingly, the claims are not anticipated by Bacon, and reconsideration and withdrawal of the rejections are respectfully requested.

Rejections Under 37 C.F.R. § 103

The Examiner also rejected Claims 3 and 5 under 37 C.F.R. § 103 as obvious over Bacon in view of U.S. Patent No. 5,957,873 ("Allen"). Claims 1, 4, 6, and 9-13 were rejected as obvious over U.S. Patent No. 6,227,203 ("Rise") in view of Bacon. Claim 24 was rejected as obvious over Bacon. Applicants respectfully traverse the rejections for the reasons provided below.

Guidance for analyzing obviousness or nonobviousness of a claimed subject matter was set forth by the U.S. Supreme Court in *Graham v. John Deere Co. of Kansas City et al.*, 86 S. Ct. 684; 15 L. Ed. 2d 545 (1966):

> "Under § 103, the scope and content of the prior art are to be determined; differences between prior art and the claims at issue are to be

> ascertained; and the level of ordinary skill in the pertinent art resolved. Against this background, the obviousness or nonobviousness of the subject matter is determined. Such secondary considerations as commercial success, long felt but unsolved needs, *failure of others*, etc., might be utilized to give light to circumstances surrounding the origin of the subject matter sought to be patented." *Id.* at 17-18, 86 S. Ct. 684, 15 L. Ed. 2d 545 (emphasis added).

Applicants' amended claims are specifically directed to coverage of a method of treating an impaired neurological function in a brain-injured individual comprising administering to the individual an effective amount of modafinil in conjunction with a neurorehabilitation program. As noted earlier, prior combinations failed to provide an effective treatment, as in the case of traditional stimulant + neurorehabilitation methods, or presented risks to the patient that essentially foreclosed unrestricted, repetitive, or chronic use of such methods, as in the case of levodopa + neurorehabilitation programs. Applicants' claimed method is effective, safer, and more useful than the ineffective traditional stimulant + physiotherapy method or the self-limiting and risk-enhancing levodopa + physiotherapy method. As noted above in *Graham*, Applicants' success in view of the failure of others in the field is a significant indication that Applicants' claimed invention is nonobvious.

With respect to rejection of Claims 3 and 5 as being obvious over Bacon in combination with Allen, Applicants respectfully traverse. As explained above, Bacon does not teach or suggest Applicants' claimed method and therefore does not teach or suggest the additional embodiments of Claim 1 found in dependent Claim 3 (specifying various neurorehabilitation programs) and dependent Claim 5 (specifying various neurostimuli of neurorehabilitation programs). In addition, nowhere does Bacon teach or suggest that modafinil should be combined with neurorehabilitation programs, let alone the method of Allen, to arrive at Applicants' claimed invention. Allen mentions that traditional treatments for patients suffering from neurological disorders include physical and occupational therapy, orthopedic bracing and surgery, speech training, physical exercises, massage, deep-pressure therapy, and compression and support orthotics (Background of the Invention, Allen). However, as with Bacon, nowhere does Allen guide persons of ordinary skill in the art to administer modafinil in conjunction with such "traditional treatments" to arrive at Applicants' claimed invention. But for reading Applicants' own specification and the perspective it provides for reasoning with hindsight, there is no reason or motivation for persons of ordinary skill in the art to combine Bacon with Allen in order to arrive at Applicants' claimed invention. Without a permissible basis for combining Bacon with Allen, there is no support for a *prima facie* case of obviousness of Claims 3 and 5. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejections.

With respect to rejection of Claims 1, 4, 6, and 9-13, as being obvious over Rise in view of Bacon, Applicants respectfully traverse. Rise describes a method of *reducing* abnormal involuntary movements (AIM) such as develop in Parkinson's Disease patients that have received chronic levodopa therapy (levodopa-induced dyskinesis). In particular, in the method of Rise, a patient is provided an implantable pump to administer a drug directly into the brain and an implantable electrode to deliver an electrical current to a neuronal population. The goal in Rise is to specifically block the Centremedian-Parafasicularis (CM-Pf) nucleus (or complex) of the thalamus, which in turn should reduce excitation of the globus pallidus internus (GPi), which in turn should reduce AIM (see, Abstract and Column 2, lines 37-59, of Rise). Thus, the method of Rise is specifically designed to block neural activity and thereby reduce AIM in a patient, and not to stimulate and restore a neurological function that is impaired but was once possessed by a brain-injured individual. According to Applicants' specification, an "impaired" neurological function is a neurological function that was lost or diminished as the result of the brain injury (see, in the specification, page 6, lines 26-27), and the neurorehabilitation program element of the claimed invention must provide one or more stimuli designed to restore or enhance one or more impaired neurological functions of an individual (see, in the specification, page 6, lines 26-30). Clearly, AIM or a levodopa-induced dyskinesis is not a previous neurological function that the patient would seek to restore or enhance according to Applicants' claimed invention.

Moreover, although Rise teaches use of 29 specific drugs from 7 different drug classes (see, Table III, Column 2, line 37-Col. 3, line 9, of Rise) with its method of treating AIM, nowhere does Rise contemplate combining administration of modafinil. The Examiner, therefore, seeks to combine Bacon to provide the element of modafinil to the method of Rise for treating AIM. Yet, not only do Rise and Bacon fail to teach their combination, but even if combined, the sum of Rise's method for inhibiting levodopa-induced AIM and of Bacon's description of a need for and provision of a new class of substituted thioacetamides over modafinil does not lead a person of ordinary skill in the art to the specific combination therapy for treating an impaired neurological function according to Applicants' claims as amended herein. Thus, Rise and Bacon, alone or in combination, fail to provide Applicants' claimed invention and therefore fail to support a *prima facie* case of obviousness under 37 C.F.R. § 103 for Claim 1 and dependent Claims 4, 6, and 9-13. Accordingly, Applicants respectfully request that the Examiner reconsider and withdraw the rejections.

Finally, the Examiner rejected Claim 24 as obvious over Bacon. Applicants respectfully traverse. Applicants note that dependent Claim 24 specifically covers the embodiment of the method of Claim 1 wherein the brain injury sustained by the individual is a traumatic brain injury that results from a fall on a hard surface, a vehicle accident, or a strike to the head. As shown above, Bacon does not teach or suggest Applicants' method in Claim 1, as amended herein, and therefore does not teach or suggest the particular

embodiments of Claim 1 that are recited in dependent Claim 24. Accordingly, Bacon does not support a *prima facie* case of obviousness to reject Claim 24 under 37 C.F.R. § 103, and reconsider and withdrawal of the rejection is respectfully requested.

In view of the amendments to the specification and claims and all of the above comments, Applicants submit that the Examiner's rejections have been overcome or rendered moot. Accordingly, Applicants respectfully request that the Examiner enter the amendments and withdraw the rejections to pass the claims to allowance.

Respectfully submitted,

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